EMORD & ASSOCIATES P.C.

BURKE PROFESSIONAL CENTER
5282 LYNGATE COURT
BURKE, VIRGINIA 22015

1050 SEVENTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20036

PHONE: (202) 466-6937 • FAX: (202) 466-6938
WEB SITE: www.emord.com
E-MAIL: aferrenz@emord.com

May 17, 2004

VIA HAND DELIVERY
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Calcium and Kidney Stones Health Claim Petition; Docket No. 2004Q-0102

To Whom It May Concern:

Please find the attached supplemental submission for filing in the above docket.

Sincerely,

Jonathan W. Emord
Andrea G. Ferrenz
Kathryn E. Balmford

Attachments

cc: Ms. Nancy T. Crane, CFSAN, ONPLDS (Via Overnight Mail)
Dr. J. Craig Rowlands, Ph.D./DABT, CFSAN, ONPLDS (Via Overnight Mail)

2004Q-0102

SUP1

Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

In re: Qualified Health Claims (QHC)	)	
Calcium and Kidney Stones;	)	
Calcium and Urinary Stones;	)	**Docket No. 2004Q-0102**
Calcium and Kidney Stones	)	

SUPPLEMENTAL SUBMISSION OF MARINE BIO USA, INC.

Marine Bio USA, Inc. ("Petitioner") hereby supplements the record in the above-referenced proceeding with the attached scientific report by Michael John Glade, Ph.D., CNS, FACN (Exhibit A). Dr. Glade's report responds to the Comments of Dr. Khashayar Sakhaee concerning the association between calcium and reduced risk for kidney stone formation. Petitioners respectfully request that FDA consider the attached report of Dr. Glade when evaluating Dr. Sakhaee's Comments.

Respectfully submitted,

MARINE BIO USA, INC.,

By: _____
Jonathan W. Emord
Claudia A. Lewis-Eng
Andrea G. Ferrenz
Kathryn E. Balmford
Their Counsel

Emord & Associates, P.C.
5282 Lyngate Court
Burke, VA 22015
P: (202) 466-6937
F: (202) 466-4938
Email: jemord@emord.com
Date submitted: May 17, 2004

May 17, 2004

J. Craig Rowlands, Ph.D./DABT
Food and Drug Administration
CFSAN
5100 Paint Branch Parkway
HFF – 830
College Park, MD 20740-3835

Dear Dr. Rowlands:

I have examined your solicited critique of the scientific report submitted in support of the proposed qualified health claims concerning calcium intake and reduction in the risk for the development of nephrolithiasis, submitted to you on April 6, 2004, by Dr. Khashayar Sakhaee.

Dr. Sakhaee has not disputed, and therefore presumably agrees with, statements in the original scientific report that "it is apparent that dietary calcium restriction increases the risk for nephrolithiasis," "a low calcium diet as a treatment for idiopathic calcium nephrolithiasis should be abandoned" and "adequate calcium nutriture reduces the risk for nephrolithiasis." Dr. Sakhaee appears to accept those statements and focuses his objections on the findings of Curhan et al. (ref. 42, 46, 47). Even a cursory reading of Dr. Sakhaee's letter reveals that once his misperceptions of the relevant studies are identified and removed, the basis for his criticism vanishes.

For example, Dr. Sakhaee has mistakenly characterized the prospective epidemiologic studies of Curhan et al. (ref. 46, 47) as retrospective studies (a much weaker category of evidence). Of course, such mischaracterization of the evidence biases its interpretation. In addition, Dr. Sakhaee has indicated that in order for him to fully accept the findings of

Curhan et al. (ref. 46, 47), the possibility that "potential confounding factors" (such as "intake of fluids, potassium and magnesium") that may have weakened the strength of the associations reported in those papers would need to be taken into consideration. However, Dr. Sakhaee has failed to acknowledge that Curhan et al. did in fact account for those factors in their analyses. Indeed, in one of the studies (ref. 46), the analysis produced a relative risk for the development of symptomatic kidney stones of 0.74 (95% confidence interval: 0.57 – 0.97) among men with estimated daily dietary calcium intakes greater than (only) 605 mg, compared to the risk among men consuming less than 605 mg daily, *after* adjustment for potentially confounding variables (including intakes of fluid and potassium).

Dr. Sakhaee also has misunderstood the report by Curhan et al. describing the findings of the Nurses' Health Study (ref. 47). Contrary to the assertions of Dr. Sakhaee, in that 12-year prospective study, representing 903,849 person-years of observation, women who consumed more than (only) 643 mg of calcium daily experienced a significant reduction in their risk for developing nephrolithiasis, compared to the risk among women who consumed less than 488 mg daily (RR: 0.72; 95% confidence interval: 0.58 – 0.89). Similarly, women who consumed more than 1098 mg daily also experienced a significant reduction in their risk for developing nephrolithiasis, compared to the risk among women who consumed less than 488 mg daily (RR: 0.65; 95% confidence interval: 0.50 – 0.83). Again, contrary to the assertions of Dr. Sakhaee, those calculated risk ratios were adjusted for calcium supplementation as well as intakes of fluids and potassium. Only when "any" supplementation with calcium was examined separately did the consistently replicated finding of an inverse relationship between calcium intake and risk for developing nephrolithiasis not appear (in fact, risk seemed to be slightly but significantly increased by this analysis). However, it was not possible to identify the amount of daily supplemental calcium responsible for this apparent effect (even over 500 mg daily of supplemental calcium, added to the dietary intake of calcium, did not increase the risk for developing nephrolithiasis among these women). Although the possible suggestion of Curhan et al. (ref. 47) for a mechanism that could account for this paradoxical finding currently lacks sufficient supportive data, it or other explanations may be borne out by

future research. For example, it is plausible that women who self-selected calcium supplementation in larger amounts may have "coincidentally" habitually consumed inadequate amounts of nonsupplemental calcium, particularly prior to the initiation of self-supplementation, potentially predisposing them to nephrolithiasis in spite of later supplementation.

Certainly the findings of the combined retrospective studies of Curhan et al. cited by Dr. Sakhaee (*Kidney Int* 2001;59:2290-2298) are difficult to reconcile with the results of their prospective studies. Unfortunately, calcium intake was not incorporated into their retrospective models. It is noteworthy that in his latest (yet to be published) research, Dr. Sakhaee was required to employ daily dietary supplementation with 800 mg of elemental calcium (in addition to dietary calcium) in order to increase urinary calcium excretion to the apparent threshold range that might have produced increased risk for the development of nephrolithiasis in the retrospective analyses of Curhan et al. (*Kidney Int* 2001;59:2290-2298). Despite decades of investigation, a comprehensive explanation of the interactions between calcium consumption and urinary calcium excretion producing reduced risk for the development of nephrolithiasis remains elusive. Nonetheless, the main finding of a statistically, biologically and clinically significant inverse relationship between calcium intake and risk for developing nephrolithiasis remains.

In attempting to refute the suggested mechanism or mechanisms proposed by Curhan et al. (ref. 46, 47) to explain their consistent replicated findings, Dr. Sakhaee relied on an unreplicated presentation that was neither peer-reviewed nor published (Heller et al., 2000, cited by Dr. Sakhaee). Certainly, important decisions of public health policy should not be based on a report that remains unpublished 4 years later, was not peer-reviewed and is not accessible for independent evaluation by persons not in Dr. Sakhaee's employ. Obviously, the credibility of such a source is not established and cannot be taken for granted.

Nonetheless, that the suggestions put forth by Curhan et al. (ref. 46, 47) may not have been borne out by subsequent research, if such had been the case, would not in any way

invalidate their main consistent replicated peer-reviewed published findings. Perhaps biochemical or physiological processes yet to be identified or elucidated act or interact to confer on calcium intake the property of stone forming risk reduction.

As emphasized by Dr. Sakhaee, the relatively short-term interventive studies of Domrongkitchaiporn et al (ref. 50, 51, 52) do not effectively address the issue of risk reduction *per se*. However, these studies, published after peer-review and providing experimental details and data open to public scrutiny, do address Dr. Sakhaee's concern over the relationship between supplemental calcium intake and urinary calcium oxalate saturation. In fact, the reports of Domrongkitchaiporn et al. (ref. 50, 51, 52) lay Dr. Sakhaee's fears to rest. Because daily dietary supplementation with as much as 625 mg of calcium as calcium carbonate failed to affect the urinary excretion of calcium, citrate or oxalate, the urinary ratio of calcium to oxalate or urinary calcium oxalate saturation, it is clear that orally administered calcium itself does not negatively impact physiological factors that might contribute to stone forming risk.

Dr. Sakhaee's experience with dietary supplementation with citrate is interesting and suggests that perhaps an independent health claim for citrate salts and the reduction of stone forming risk can be substantiated. However, despite his interest in that issue, it is irrelevant to the proposed health claims under discussion.

Fortunately, Dr. Sakhaee's expectation that "urinary saturation of calcium oxalate would actually increase significantly with calcium carbonate" is not supported and, in fact, is contradicted by the peer-reviewed published scientific literature cited by Dr. Sakhaee. Similarly, Dr. Sakhaee's assertion that "there is no concrete evidence that a high calcium intake reduces the stone forming risk" is contradicted by the peer-reviewed published scientific literature he has discussed. Interestingly, in making this statement and others similar to it, it is apparent that Dr. Sakhaee has missed the point of the petition. It seems that he has consistently equated the amounts of calcium intake associated with reduction in the risk for developing nephrolithiasis (in 2 reports, just over 600 mg daily) with "high" intakes. Had he read it carefully he would have noticed that the amount of total

daily calcium intake being advocated in both the petition and its supporting scientific report is merely the current Dietary Reference Intakes (ref. 29).

As discussed in detail in the original scientific report, even daily dietary supplementation with calcium carbonate providing amounts of calcium far in excess of those recommended by the petition under discussion consistently have been found to be without increased risk for the development of nephrolithiasis (ref. 62-70). Although one investigator calculated a Lowest Observed Adverse Effect Level (LOAEL) for calcium for individuals with a history of nephrolithiasis of 1685 mg daily (ref. 71), that amount exceeds the recommendations of the petition under discussion. The Food and Nutrition Board of the Institute of Medicine has determined that total daily calcium intakes of up to 2500 mg (unattainable without dietary supplementation) are "unlikely to pose risks of adverse health effects to almost all individuals" over 1 year of age (ref. 29). In addition, the Board has concluded that "for the majority of the general population, intakes of calcium from food substantially above the UL are probably safe" (ref. 29). The US Food and Drug Administration has concluded that daily intakes of elemental calcium of up to at least 1800 mg pose no increased risk for kidney stones among the general population (ref. 61).

Concerning interactions between calcium intake and the physiology of calcium and its metabolism, Dr. Sakhaee has published data demonstrating that daily dietary supplementation with 1000 mg of calcium was accompanied by gradual downregulation of the fractional absorption of ingested calcium and attenuation of urinary calcium excretion (*J Urol* 1994;152:324-327) and he has written that "In most premenopausal women the risk of calcium stone formation probably is present during the first few months of calcium supplementation but not during long-term calcium response. The risk of calcium nephrolithiasis from calcium supplementation probably is low in most postmenopausal women because of the impaired intestinal absorption of calcium and blunted calciuric response" (*J Urol* 1987;137:1212-1213).

Clearly, the available relevant peer-reviewed published scientific evidence, including that provided by Dr. Sakhaee, continues to support the conclusions that

- Avoidance of the possibility of dietary calcium deficiency reduces the risk for nephrolithiasis.

- Daily intakes of calcium satisfying the current Institute of Medicine intake recommendations for this nutrient reduce the risk for nephrolithiasis.

- Routine chronic consumption of dietary and supplemental calcium in amounts consistent with the current Institute of Medicine recommendations for this nutrient is safe.

- Calcium may reduce the risk of kidney stones.

- Calcium may reduce the risk of urinary stones.

Sincerely yours,

[signature on file]_____
Michael J. Glade, Ph. D.

Attachment

Additional Literature Cited

Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int* 2001;59:2290-2298.

Sakhaee K, Baker S, Zerwekh J, Poindexter J, Garcia-Hernandez PA, Pak CY. Limited risk of kidney stone formation during long-term calcium citrate supplementation in nonstone forming subjects. *J Urol* 1994;152:324-327.

Pak CY, Sakhaee K, Hwang TI, Preminger GM, Harvey JA. Nephrolithiasis from calcium supplementation. *J Urol* 1987;137:1212-1213).